NKR 55 PICO 5 Seponering af antidepressiva

Review information

Authors

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Citation example: S. NKR 55 PICO 5 Seponering af antidepressiva. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Characteristics of studies

Characteristics of included studies

Bergh 2012

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention ● *No of males (%)*: 14 (22) ● *Mean age (SD)*: 85.3 (8.2) Control ● *No of males (%)*: 18 (28) ● *Mean age (SD)*: 86.1 (6.7) Overall ● *No of males (%)*: ● *Mean age (SD)*: **Included criteria:** Patients who were diagnosed with dementia in Alzheimer's disease, vascular dementia, or a mixture of Alzheimer's disease and vascular dementia (as defined by ICD-10 (international classification of diseases, 10th revision, diagnostic criteria forresearch) were included; had been nursing home residents for more than four weeks; had

	a neuropsychiatric symptom; and were prescribed a selective serotonin reuptake inhibitor (escitalopram, citalopram, sertraline, or paroxetine) for at least three months.No changes in the dose of the current antidepressant treatment were allowed in the last four weeks before inclusionand throughout the study period. Changes in the prescription of psychotropic drugs other than antidepressants during the study period were allowed. **Excluded criteria:** Disorder or schizophrenia, severe somatic disease or terminal illness, or an inability to take tablets or capsules as prescribed.The exclusion of people with a documented depressive disorder was based on interviews with the nursing home doctors as well as studying the patients' medical records. Exclusion of patients with severe physical illness was based on ethical reasons and the assumption that they would not complete a study period of 25 weeks. **Pretreatment:** No significant differences between the two groups at baseline, in terms of sex, age, the clinical dementia rating scale, dementia diagnosis, the Cornell scale, or the neuropsychiatric inventory were seen.
Interventions	**Intervention Characteristics** Intervention (Discontinuation group) ● *Desrciption*: randomised, placebo controlled discontinuation trial of fourselective serotonin reuptake inhibitors (escitalopram, citalopram,sertraline, and paroxetine), done in 52 nursing homes in Norway,independently of any pharmaceutical company. At the first weekafter baseline assessment, the antidepressants were taperedoff and replaced by a placebo (discontinuation group) ● *Duration*: 25 weeks ● *Dose*: Placebo, no active drug Control (Continuation group) ● *Desrciption*: Randomised, placebo controlled discontinuation trial of fourselective serotonin reuptake inhibitors (escitalopram, citalopram,sertraline, and paroxetine), done in 52 nursing homes in Norway,independently of any pharmaceutical company. At the first week after baseline assessment, the antidepressants were replacedby a study drug containing active medication with the samesubstance and same dose as before inclusion (continuation group). ● *Duration*: 25 weeks ● *Dose*: The same substance and same dose as before inclusion
Outcomes	*Depressive symptomer_Cornell scale (0-38)* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Fully reported ● **Scale**: Cornell scale for depression in dementia ● **Range**: 0-38 ● **Unit of measure**: scale

- **Direction**: Lower is better
- **Data value**: Endpoint

BPSD_Neuropsychiatric inventory agitation total score

- **Outcome type**: ContinuousOutcome
- **Reporting**: Fully reported
- **Scale**: Neuropsychiatric inventory
- **Unit of measure**: scale
- **Direction**: Lower is better
- **Data value**: Endpoint

Kognitiv funktion_Severe impairment battery (SIB)(0-100)

- **Outcome type**: ContinuousOutcome
- **Reporting**: Fully reported
- **Scale**: Severe impairment battery (SIB)
- **Range**: 0-100
- **Unit of measure**: Scale
- **Direction**: Higher is better
- **Data value**: Endpoint

Alvorlige bivirkninger (SAE)

- **Outcome type**: DichotomousOutcome
- **Reporting**: Fully reported
- **Scale**: Death, somatic disease, or admitted to hospital
- **Unit of measure**: number
- **Direction**: Lower is better
- **Data value**: Endpoint

Livskvalitet_Quality of life-Alzheimer's disease scale, patients' rating

- **Outcome type**: ContinuousOutcome
- **Reporting**: Fully reported
- **Scale**: Severe impairment battery (SIB)
- **Range**: 13-52
- **Unit of measure**: Scale
- **Direction**: Higher is better

	● **Data value**: Endpoint
Identification	**Sponsorship source:** The study was funded by unrestricted grants from the Innlandet Hospital Trust, the Research Council of Norway, and the South-Eastern Norway Regional Health Authority. **Country:** Norway **Setting:** Norwegian nursing homes; residents recruited by 16 study centres in Norway from August 2008 to June 2010. **Comments:** Trial registration: ClinicalTrial.gov NCT00594269 **Authors name:** Sverre Bergh **Institution:** Centre for Old Age Psychiatric Research, Innlandet Hospital Trust **Email:** sverre.bergh@sykehuset-innlandet.no **Address:** N-2312 Ottestad, Norway
Notes	Personer med demens og BPSD, men ikke depression. Skal have været i behandling med antidepressiva min. 3 mdr. Antidepressiva seponeres hos 63 og fortsættes hos 68. Opfølgning ved baseline, uge 4, 7, 13 og 25. Har flere relevante outcomes med (depressions-score, NPI, kognitiv funktion ved SIB og QoL), men kun data fra uge 25 præsenteres.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We used computer generated randomisation (1:1) in blocks of four."
Allocation concealment (selection bias)	Low risk	Quote: "Packing of study treatment was done at the Hospital Pharmacy at the Innlandet Hospital Trust, and was kept hidden, by the use of blank labels, from the participants, caregivers, and the assessors until the completion of data collection and statistical analyses. Randomisation was done across study"
Blinding of participants and personnel (performance bias)	Low risk	Quote: Randomisation and masking. We used computer generated randomisation (1:1) in blocks of four. Packing of study treatment was done at the Hospital Pharmacy at the Innlandet Hospital Trust, and was kept hidden, by the use of blank labels, from the participants, caregivers, and the assessors until the completion of data collection and statistical analyses. Randomisation was done across study centres" Judgement Comment: Participants and personnel were blinded

Blinding of outcome assessment (detection bias)	Low risk	Quote: "Packing of study treatment was done at the Hospital Pharmacy at the Innlandet Hospital Trust, and was kept hidden, by the use of blank labels, from the participants, caregivers, and the assessors until the completion of data collection and statistical analyses. Randomisation was done across study centres and facilities." Judgement Comment: Outcome assessors were blinded
Incomplete outcome data (attrition bias)	High risk	Quote: "We excluded 11 patients (four in the discontinuation group and seven in the continuation group) from the efficacy analyses, either because no post baseline assessments were available or because of study protocol violation; therefore, we included 117 patients for the efficacy analysis. Forty seven (37%) patients withdrew from the study prematurely, 28 (44%) in the discontinuation group and 19 (29%) in the continuation group. The only reason for drop outs that differed significantly between groups was an increase in neuropsychiatric symptoms, for 13 (21%) patients in the discontinuation group and four (6%) in the continuation group (table 2⇓).Efficacy analyses Table 3⇓ presents" Judgement Comment: We included all patients in the safety analysis, and all patients with at least one assessment after the baseline (n=117) in the efficacy analysis. We analysed patients with complete data(n=81) for changes in the primary and secondary endpoints using analysis of covariance, presented as observed cases- Judgement Comment: High risk due to incomplete data.
Selective reporting (reporting bias)	Low risk	Quote: "The trial was registered in ClinicalTrial.gov on 3 January 2008 (NCT00594269)." Data were assessed at baseline, four, seven, 13 and 25 weeks and only data from week 25 are reported and prespecified in the protocol.
Other bias	Low risk	Judgement Comment: The study appears to be free of other sources of bias

Nyth 1990

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall ● *No of males (%)*: 20 (22.5) ● *Mean age (SD)*: 77.6 **Included criteria:** To be included, the patients had at least to be able to help in undressing and dressing themselves and

	in taking food (less than five points on items M1 and M2 of the Gottfries-Bråne-Sten (GBS) geriatric rating scale. The inclusion criteria further permitted only one of the following items to be scored six: orientation in space,orientation in time or personal orientation (items Ii, 12 and 13 of the GBS scale). The maximum score of recent and distant memory (14 and IS of the GBS scale) had to be four, while the minimum score of recent memory had to be two (mild to moderate disturbance). **Excluded criteria:** Patients with severe dementia were not included.Patients who suffered from serious somatic illnesses (like cardiac decompensation and malignant arrhythmias, renal insufficiency, liver dysfunction, general gastrointestinal malabsorption, or disease of the haematopoietic system), those with a history of schizophrenia, epilepsy, alcoholismor drug dependence and those who had recently been treated with monoamine oxidase inhibitors were excluded. **Pretreatment:** Significant differences at baseline in GBS-rating scale in Irritability (item 22) and Depressed mood (item 25), Figure 2.
Interventions	**Intervention Characteristics** Intervention ● *Desrciption*: The trial consisted of three periods of treatment (A, B and C) and was carried out over 16 weeks (Fig. 1). All patients were initially given placebo for one week (wash-out period). The patients were then randomly assigned to double-blind treatment with either citalopram or placebo during four weeks. This A-period was followed by eight weeks of treatment with citalopram as a known substance (B-period).The B-period was included for ethical reasons since we wanted to give all the patients the opportunity to be treated with active substance. Finally, the patients once more were randomly assigned to double-blind treatment during fourweeks with either citalopram or placebo (C-period). The second randomisation was independent of the first one. The C-period was included to check withdrawal symptoms with a double-blind technique. ● *Duration*: 4 weeks (C-period) ● *Dose*: The patients received tablets of identical appearance each containing either 10mg citalopram or inactive substance. During the first two weeks of the treatment, two tablets (either 20mg citalopram or placebo) were given daily at about 4p.m. to each patient.If there was no satisfactory treatment effect at the beginningof the third week, the dose was increased to three tabletsdaily (either 30mg citalopram or placebo). The dose wasdecreased to one tablet (either 10mg citalopram or placebo)if there were troublesome adverse side-effects. There wereno changes in medication if the therapeutic effect wassatisfactory. At the beginning of the B-period the initialdose was 20mg citalopram. After some days this dose couldbe changed according to the previous treatment orconsideration by the doctor in charge to 30 or 10mgcitalopram. The same dose was then kept constant duringthe rest of the trial unless there were any adverse effects. Additional medication was allowed to treat concurrentsomatic diseases. Necessary treatment with hypnotics andsedatives was also permitted.

	Control ● *Desrciption*: The trial consisted of three periods of treatment (A, B and C) and was carried out over 16 weeks (Fig. 1). All patients were initially given placebo for one week (wash-out period). The patients were then randomly assigned to double-blind treatment with either citalopram or placebo during four weeks. This A-period was followed by eight weeks of treatment with citalopram as a known substance (B-period).The B-period was included for ethical reasons since we wanted to give all the patients the opportunity to be treated with active substance. Finally, the patients once more were randomly assigned to double-blind treatment during fourweeks with either citalopram or placebo (C-period). The second randomisation was independent of the first one. The C-period was included to check withdrawal symptoms with a double-blind technique. ● *Duration*: 4 weeks (C-period) ● *Dose*: The patients in the study received tablets of identical appearance. In the control group the tablets contained inactive substance. The dose wasdecreased to one tablet if there were troublesome adverse side-effects. There wereno changes in medication if the therapeutic effect wassatisfactory. Additional medication was allowed to treat concurrentsomatic diseases. Necessary treatment with hypnotics andsedatives was also permitted.
Outcomes	No data available
Identification	**Sponsorship source:** Not reported **Country:** Sweden, Norway and Finland **Setting:** Hospitals and nursing home **Comments:** The Ethical Committees of the various researchcentres and the national health authorities approved thesebiochemical investigations. **Authors name:** Anna Lena Nyth **Institution:** University of Göteborg, Department of Psychiatry and Neurochemistry **Email:** not available **Address:** St Jörgen's Hospital, S-422 03 Hisings-Backa, Sweden
Notes	Inkluderer 98 patienter med AD eller VD. Ekskluderer patienter med meget svær demens. Studiedesign: 1 uges 'wash-out', 4 uger med randomisering til placebo eller citalopram efterfulgt af 8 ugers openlabel behandling med citalopram. Til sidst randomiseres patienterne igen til placebo eller citalopram i 4 uger. Der rapporteres ikke om seponerings-symptomer i sidste fase. Det er beskrevet, at der i 'seponeringsfasen' både var forbedring og forværring på flere skalaer - men ingen data præsenteres.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were then randomly assigned to double-blind treatment with either citalopram or placebo during four weeks." Judgement Comment: It is unclear how the randomisation was performed Insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information provided
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "symptoms with a double-blind technique. With regard to drug administration, the patients received tablets of identical appearance each containing either 10mg citalopram or inactive substance. During the first two weeks" Judgement Comment: No description of blinding of personnell. However it is assumed that the personnel were not aware of the containing of the tablets
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: The study is double blinded, but it is unclear if the outcome assessors are blinded
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: 9 participants withdrew from the study phase A and were not included in the efficacy analyses. 3 participants withdrew during phase B and C.
Selective reporting (reporting bias)	Unclear risk	Judgement Comment: No pre-specified protocol availaable
Other bias	Low risk	Judgement Comment: The study appears to be free of other sources of bias

Footnotes

Characteristics of excluded studies

Garfinkel 2018

Reason for exclusion	Wrong study design

Thompson 2007

Reason for exclusion	Wrong study design

Ulfvarson 2003

Reason for exclusion	Wrong patient population

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

References to studies

Included studies

Bergh 2012

Bergh, Sverre; Selbaek, Geir; Engedal, Knut. Discontinuation of antidepressants in people with dementia and neuropsychiatric symptoms (DESEP study): double blind, randomised, parallel group, placebo controlled trial.. BMJ 2012;344(Journal Article):e1566. [DOI: https://dx.doi.org/10.1136/bmj.e1566]

Nyth 1990

Nyth, A. L.; Gottfries, C. G.. The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. A Nordic multicentre study.. British Journal of Psychiatry 1990;157(Journal Article):894-901. [DOI:]

Excluded studies

Garfinkel 2018

Garfinkel, D.. Poly-de-prescribing to treat polypharmacy: efficacy and safety.. Therapeutic Advances in Drug Safety 2018;9(1):25-43. [DOI: http://dx.doi.org/10.1177/2042098617736192]

Thompson 2007

Thompson, Sarah; Herrmann, Nathan; Rapoport, Mark J.; Lanctot, Krista L.. Efficacy and safety of antidepressants for treatment of depression in Alzheimer's disease: a metaanalysis.. Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie 2007;52(4):248-255. [DOI:]

Ulfvarson 2003

Ulfvarson, Johanna; Adami, Johanna; Wredling, Regina; Kjellman, Bengt; Reilly, Marie; von Bahr, Christer. Controlled withdrawal of selective serotonin reuptake inhibitor drugs in elderly patients in nursing homes with no indication of depression.. European journal of clinical pharmacology 2003;59(10):735-740. [DOI:]

Other references

Additional references

Other published versions of this review

Classification pending references

Data and analyses

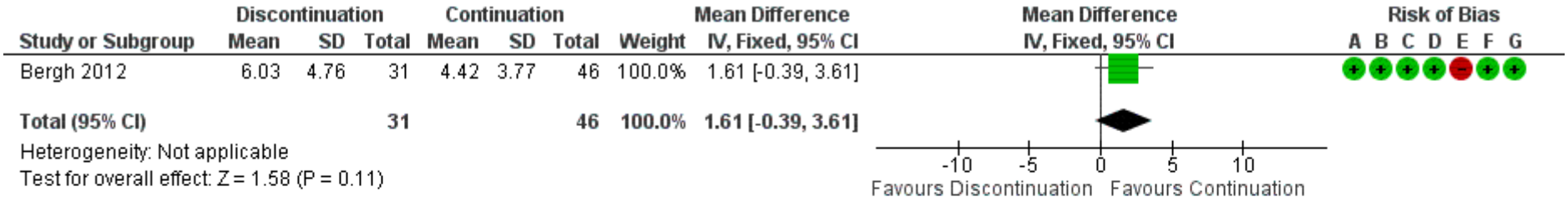
1 Discontinuation vs Continuation

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Depressive symptomer_Cornell scale (0-38)_End of treatment	1	77	Mean Difference (IV, Fixed, 95% CI)	1.61 [-0.39, 3.61]

1.2 BPSD_Neuropsychiatric inventory_total score_End of treatment	1	81	Mean Difference (IV, Fixed, 95% CI)	7.80 [2.00, 13.60]
1.3 Kognitiv funktion_Severe impairment battery (SIB)(0-100)_End of treatment	1	60	Mean Difference (IV, Fixed, 95% CI)	-5.38 [-19.35, 8.59]
1.4 Livskvalitet_Quality of life-Alzheimer's disease scale, patients' rating_End of treatment	1	51	Mean Difference (IV, Fixed, 95% CI)	3.07 [-0.50, 6.64]
1.5 Livskvalitet_Quality of life-Alzheimer's disease scale, caregivers' rating_End of treatment	1	80	Mean Difference (IV, Fixed, 95% CI)	-0.78 [-3.42, 1.86]
1.6 Alvorlige bivirkninger (SAE)_End of treatment	1	128	Risk Ratio (IV, Fixed, 95% CI)	1.03 [0.38, 2.77]

Figures

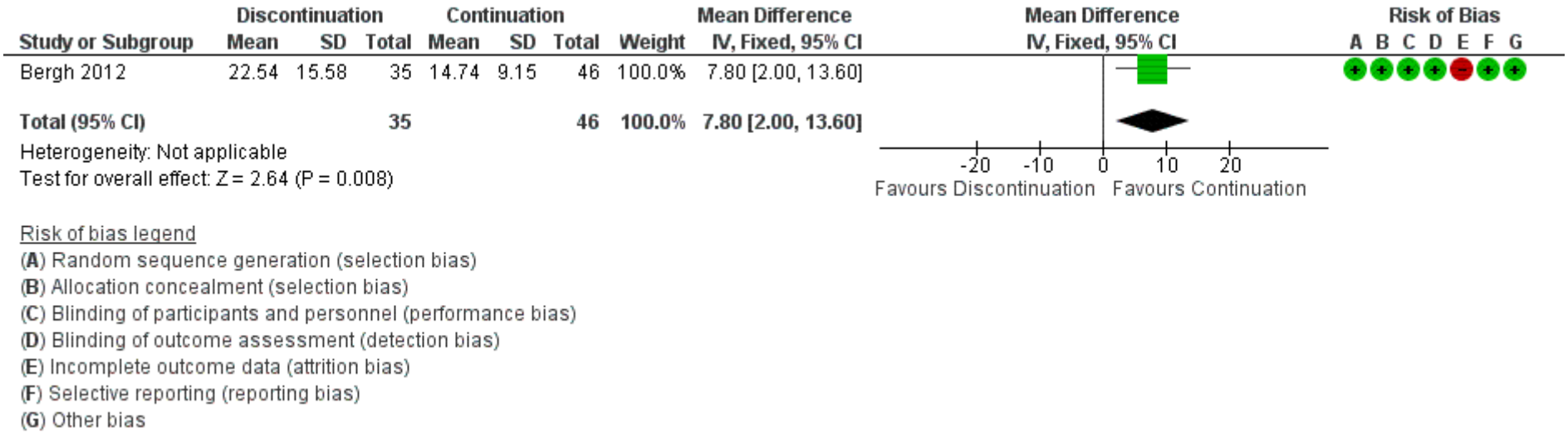
Figure 1 (Analysis 1.1)



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

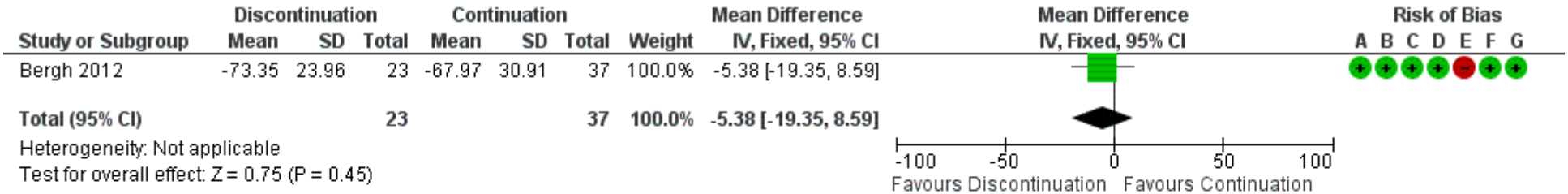
Forest plot of comparison: 1 Discontinuation vs Continuation, outcome: 1.1 Depressive symptomer_Cornell scale (0-38)_End of treatment.

Figure 2 (Analysis 1.2)



Forest plot of comparison: 1 Discontinuation vs Continuation, outcome: 1.2 BPSD_Neuropsychiatric inventory_total score_End of treatment.

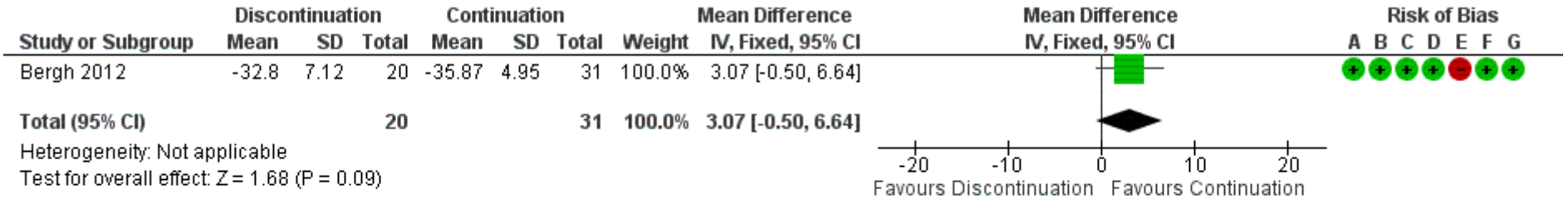
Figure 3 (Analysis 1.3)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Discontinuation vs Continuation, outcome: 1.3 Kognitiv funktion_Severe impairment battery (SIB)(0-100)_End of treatment.

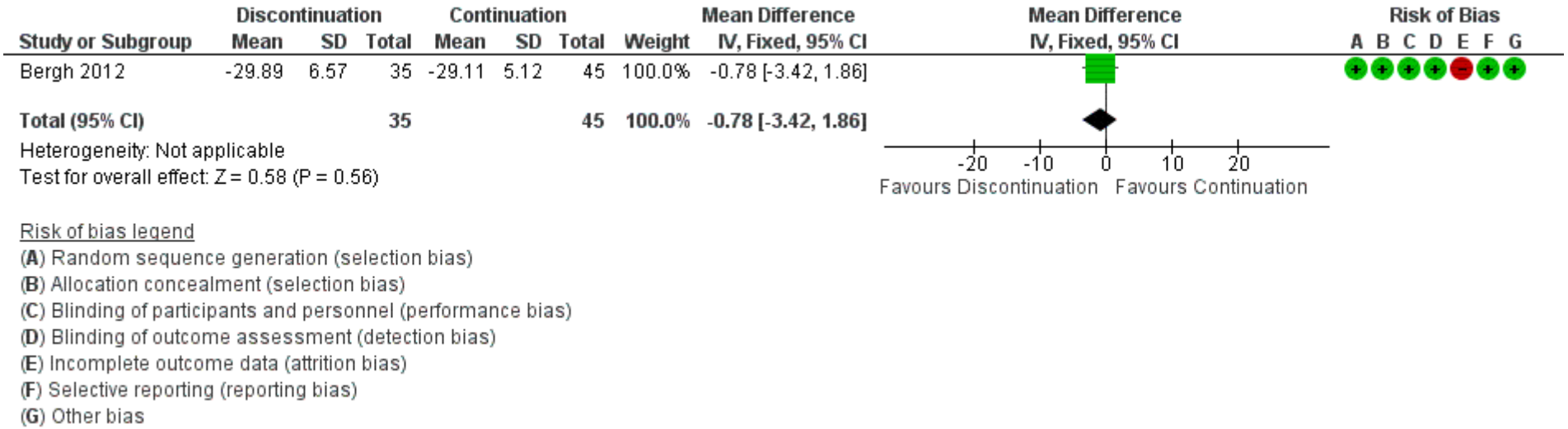
Figure 4 (Analysis 1.4)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

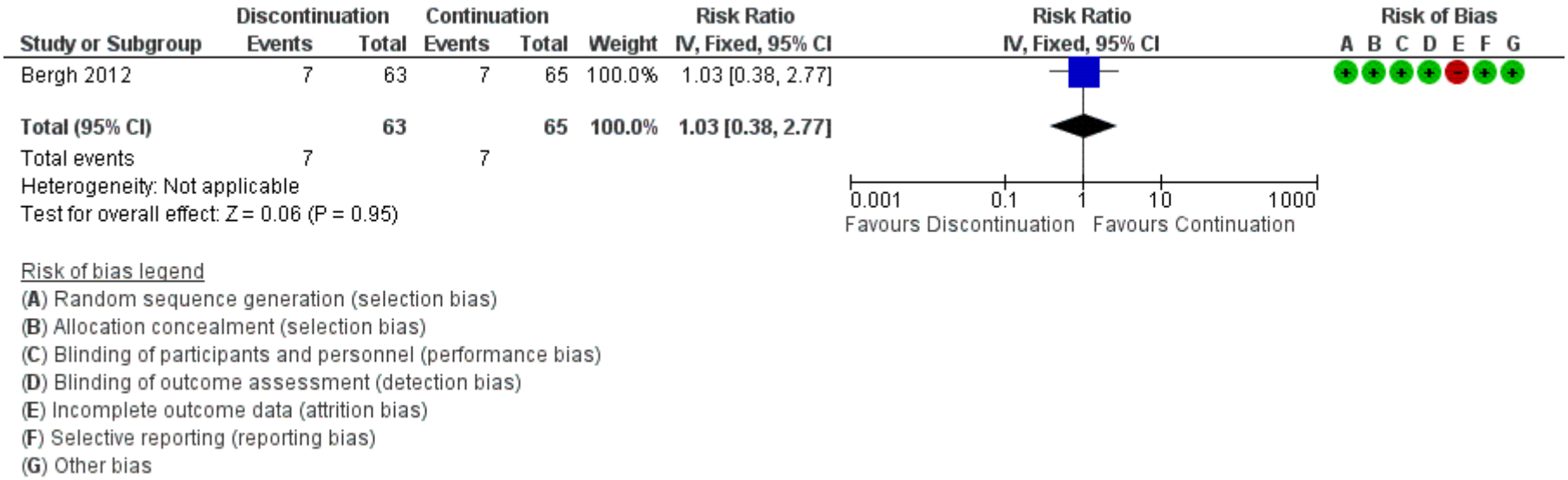
Forest plot of comparison: 1 Discontinuation vs Continuation, outcome: 1.4 Livskvalitet_Quality of life-Alzheimer's disease scale, patients' rating_End of treatment.

Figure 5 (Analysis 1.5)



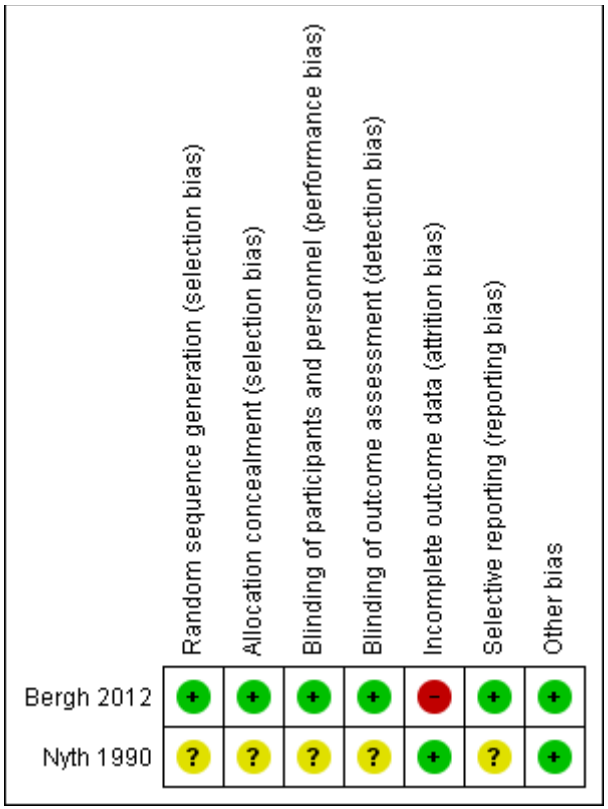
Forest plot of comparison: 1 Discontinuation vs Continuation, outcome: 1.5 Livskvalitet_Quality of life-Alzheimer's disease scale, caregivers' rating_End of treatment.

Figure 6 (Analysis 1.6)



Forest plot of comparison: 1 Discontinuation vs Continuation, outcome: 1.6 Alvorlige bivirkninger (SAE)_End of treatment.

Figure 7



Risk of bias summary: review authors' judgements about each risk of bias item for each included study.